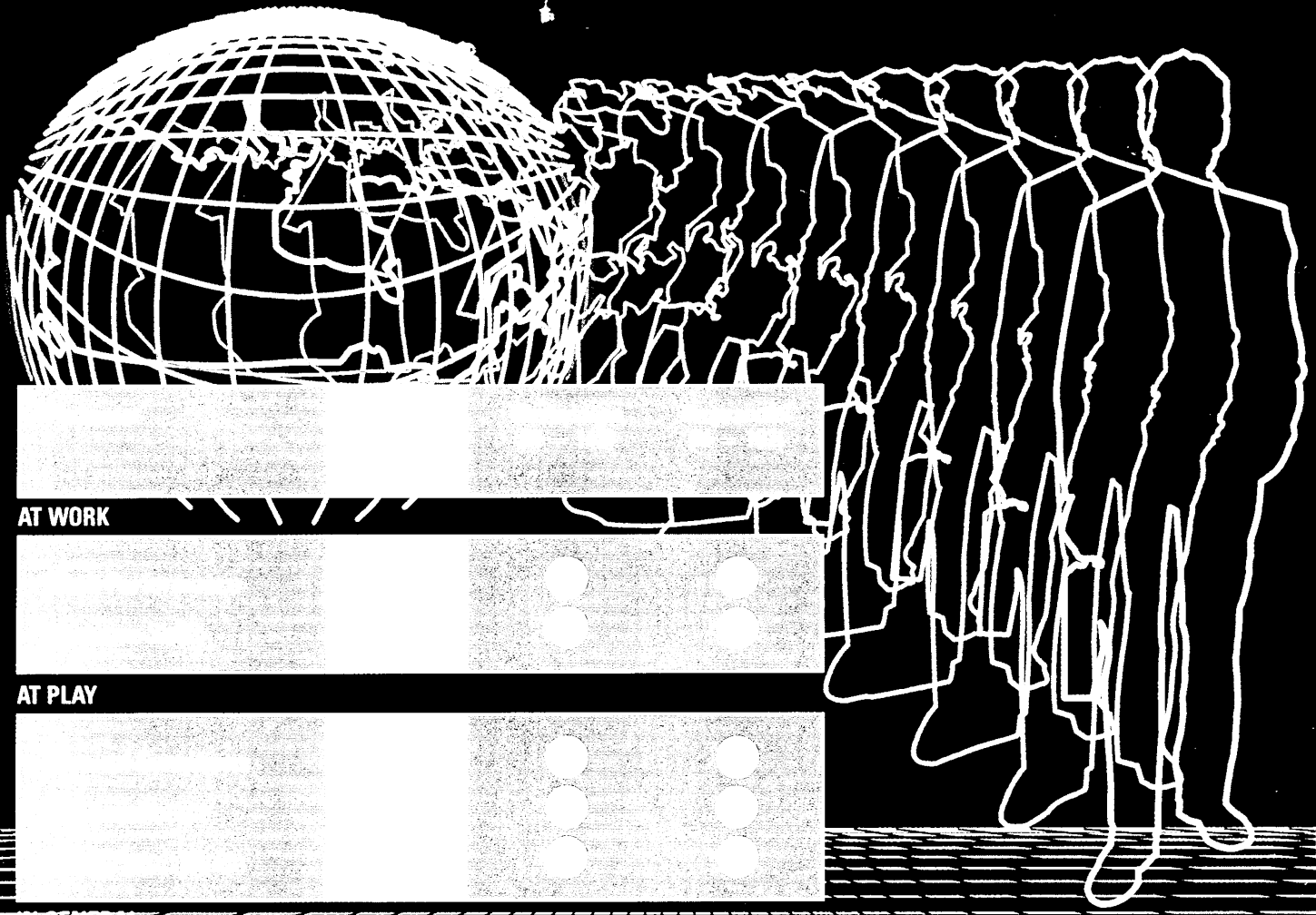
THE CAPOTEN REVOLUTION

More and more Canadian physicians are turning to Capoten...

for efficacy with minimal effect on lifestyle in newly diagnosed hypertensive patients, if traditional therapy is unacceptable*



Changes in patient lifestyle during active therapy with Capoten, methyldopa and propranolol (30-centre, randomized, double-blind, 24-week study)[1]

● Improved**
● Stable
● Worsened**

**Statistically significant change, compared to pre-treatment

SQUIBB
Innovators in cardiovascular medicine

CAPOTEN®
(captopril)
The World's #1 ACE Inhibitor†

PRESCRIBE CAPOTEN NO SUBSTITUTION

Reference: 1. Croog SH et al.: The Effects of Antihypertensive Therapy on the Quality of Life. New Engl J Med 314(26):1657-64 (1986).

†Based on worldwide sales of ACE inhibitors

*Please consult product monograph before prescribing.

PAAB

EFFECTIVE SUPPRESSION OF VIRAL EXPRESSION

(acyclovir)

℗ZOVIRAX*

TABLETS • OINTMENT • I.V. INFUSION

TO CONTROL THE HERPES SIMPLEX VIRUS

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KIRKLAND, QUÉ

Product Monograph available on request

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ZOV-8810

PAAB
CCPP

NOW —
the next generation potassium supplement.

K-DUR 20 | Microburst Release System

(potassium chloride)
20 mEq (mmol) 1500 mg
Sustained-Release Tablets

The only tablet... to deliver 20 mEq of potassium chloride in a single dose.

The only tablet... to offer single-tablet convenience for once-daily maintenance therapy.

The only tablet... that can be swallowed whole, halved or suspended in liquid for maximum dosage flexibility.

The only tablet... to provide the safety margin and bioavailability of a liquid, without the bitter taste.

KEY PHARMACEUTICALS

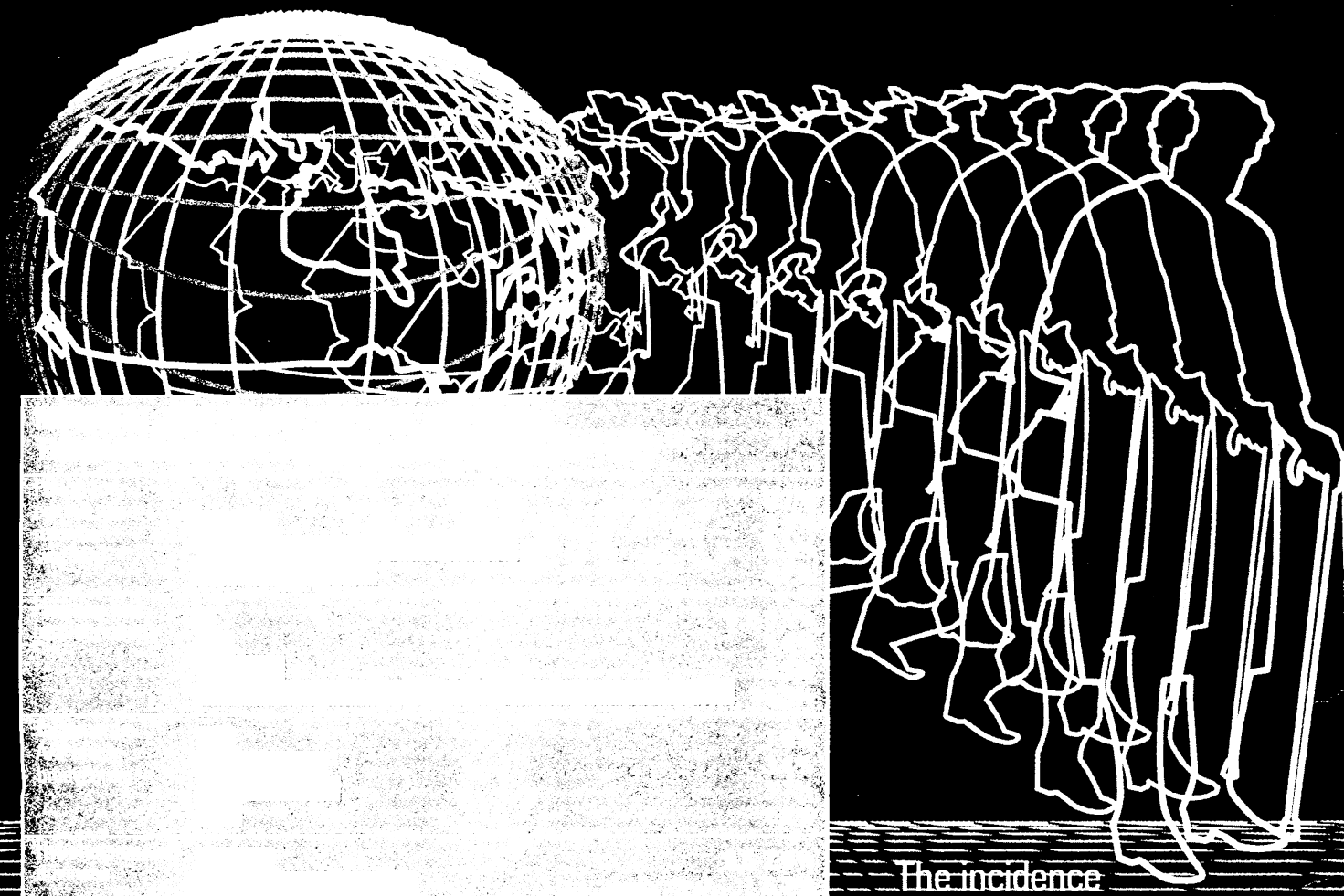
...at the leading edge of pharmaceutical technology.

*Trademark

THE CAPOTEN REVOLUTION

More and more Canadian physicians are turning to Capoten...

for efficacy with minimal effect on patient lifestyle[1] vs. calcium antagonists[2,3,4] in elderly hypertensive patients



The incidence of adverse effects with calcium channel blockers can be significantly higher in elderly patients.[2,3,4]

*Adverse effects such as taste disturbances (2%) and skin rash (7%) are associated with Capoten; these are usually reversible and self-limiting.[5]

CAPOTEN* (captopril)
Sustained release verapamil HCl
Sustained release diltiazem HCl
Prolonged action nifedipine

SQUIBB
Innovators in cardiovascular medicine

CAPOTEN®
(captopril)
The World's #1 ACE Inhibitor†

PRESCRIBE CAPOTEN NO SUBSTITUTION

References: 1. Williams GH. Converting-enzyme inhibitors in the treatment of hypertension. *N Engl J Med* 1988 Dec 319(23):1517-25. 2. Nifedipine Prescribing Information. *Compendium of Pharmaceuticals and Specialties*, Can. Pharm. Ass. 23rd Edit. (1988). 3. Verapamil Prescribing Information, G.D. Searle and Company of Canada, Limited (1988). 4. Diltiazem Prescribing Information, Nordic Laboratories Inc. (1988). 5. Capoten Prescribing Information.

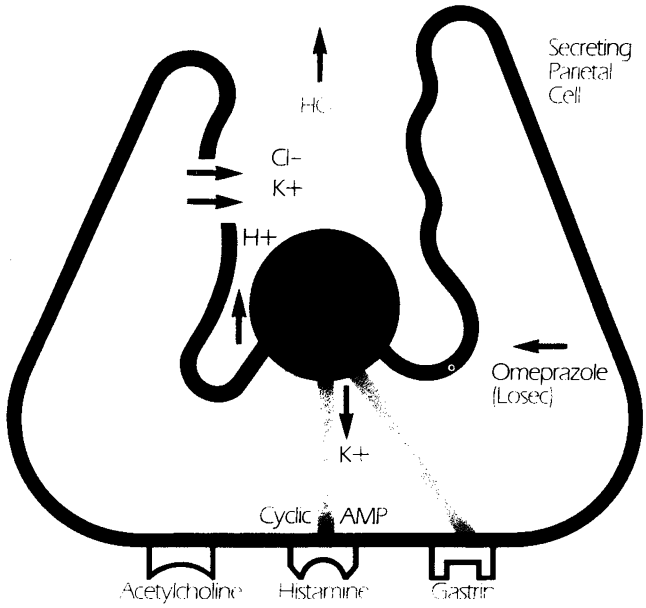
†Based on worldwide sales of ACE inhibitors

PAAB

INTRODUC

The first acid

Precise action, consistent control of gastric acid.



Losec inhibits the final common pathway of acid production – the acid pump!

It is now very well established that inhibiting gastric acid secretion effectively heals ulcers and reduces acid-related symptoms.

Losec® controls acid at its source the acid pump of the parietal cell located in the oxyntic glands of the gastric mucosa![1]

Since the acid pump is the final common pathway for gastric acid secretion, Losec inhibits acid more effectively than ranitidine and cimetidine![2]

Significantly superior healing rates, faster freedom from pain.

In well-controlled studies, patients felt better sooner with Losec.

With good reason.

Compared with ranitidine, healing rates in duodenal ulcer, gastric ulcer, and reflux esophagitis were endoscopically proven to be significantly superior![3-5]

ING LOSEC®
pump inhibitor. (omeprazole)

Proven safety profile.

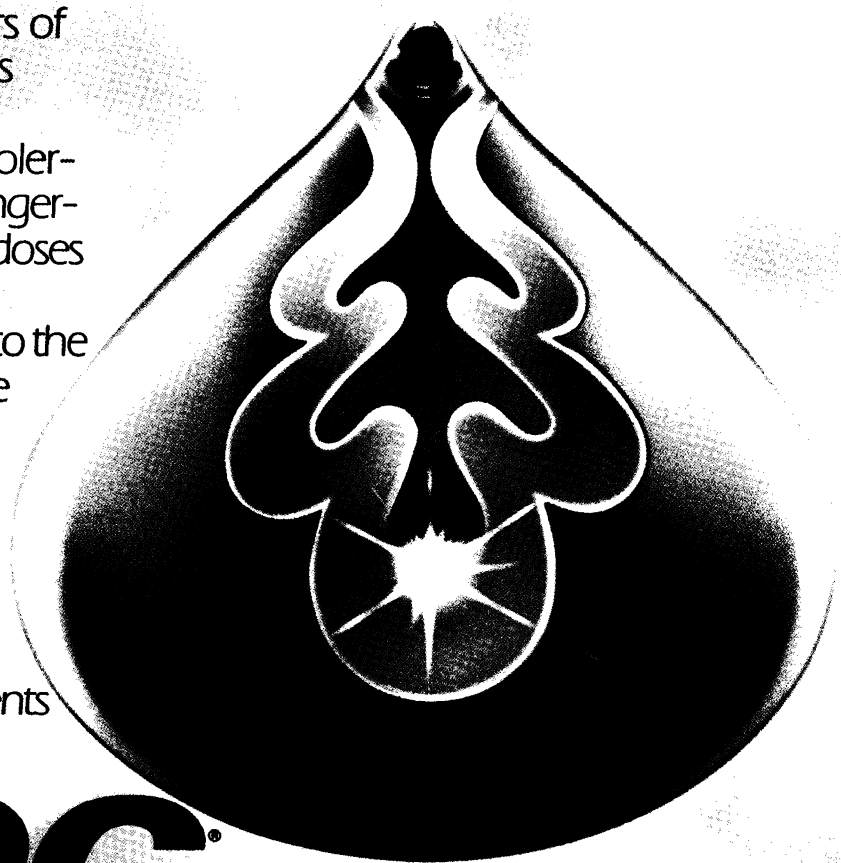
The safety profile of Losec has been established in seven years of studies involving 13,000 patients and healthy volunteers.[6]

Losec was generally well tolerated including patients with Zollinger-Ellison Syndrome receiving high doses for up to 5 years.[6]

Since Losec is highly specific to the acid pump and becomes active only in the high acidity of the parietal cell, its side effect profile is low.[6]

Losec is a new beginning in the treatment of gastric acid related disorders.

The time to start your patients on Losec is now.



Losec®

(omeprazole)

LOSEC®
FULL DISCLOSURE DOCUMENT
Effective June 1989-June 1991

Losec® (OMEPRAZOLE)

THERAPEUTIC CLASSIFICATION

H^+, K^+ –ATPase Inhibitor

Action:

LOSEC (omeprazole) inhibits the gastric enzyme H^+, K^+ –ATPase (the proton pump) which catalyzes the exchange of H^+ and K^+. It is effective in the inhibition of both basal acid secretion and stimulated acid secretion. The inhibition is dose dependent. Daily oral doses of 20 mg LOSEC and higher, showed a consistent and effective acid control. A mean reduction of 24 hour intragastric acidity of approximately 80% was achieved during repeated dosing of 20 mg daily.

LOSEC is absorbed rapidly. After an initial oral dose of LOSEC, approximately 35% of the drug is absorbed from the gastrointestinal tract. Following one week of therapy, the percentage absorbed is 43. Neither food nor antacids have any effect on the bioavailability. Peak plasma levels occur within about 4 hours. The terminal plasma half-life is about 40 minutes. Although the antisecretory effect of omeprazole is directly proportional to the AUC, it is not dependent on the plasma concentration at any given time. Omeprazole is 95% bound to plasma proteins.

Omeprazole undergoes an extensive first-pass metabolism. Following I.V. and oral administration, 80% of the dose is recovered as urinary metabolites, the remaining 20% is excreted in the feces.

Indications and Clinical Use:

LOSEC is indicated in the treatment of conditions where a reduction of gastric acid secretion is required, such as:

1) duodenal ulcer
2) gastric ulcer
3) reflux esophagitis
4) Zollinger-Ellison Syndrome (pathological hypersecretory conditions)

Contraindications:

Hypersensitivity to omeprazole or any of the components of this medication.

Warnings:

When gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with LOSEC is instituted as treatment with LOSEC may alleviate symptoms and delay diagnosis.

Use in Pregnancy: The safety of LOSEC in pregnancy has not been established. LOSEC should not be administered to pregnant women unless the expected benefits outweigh the potential risks.

Nursing Mothers: It is not known if LOSEC is secreted in human milk. LOSEC should not be given to nursing mothers unless its use is considered essential.

Use in Children: The safety and effectiveness of LOSEC in children has not yet been established.

Precautions:

Use in the Elderly: Elderly subjects showed increased bioavailability (79%), reduced total plasma clearance (229 mL/min) and prolonged (50%) elimination half-life. The daily dose in elderly patients should, as a rule, not exceed 20 mg (see DOSAGE AND ADMINISTRATION).

Patients with Hepatic Insufficiency: Patients with impaired liver function showed an increased bioavailability (to 97%), reduced total plasma clearance (75 mL/min), and a four-fold prolongation of the elimination half-life (2.7 hours). Twenty mg given once daily to these patients for 4 weeks was well tolerated, with no accumulation of omeprazole or its metabolites. The daily dose in patients with severe liver disease should, as a rule, not exceed 20 mg (see DOSAGE AND ADMINISTRATION).

Patients with Renal Insufficiency: The disposition of intact LOSEC is unchanged in patients with impaired renal function and no dose adjustment is needed in these patients (see DOSAGE AND ADMINISTRATION).

Carcinogenicity: The rat carcinogenicity study (24 months) revealed a gradual development from gastric ECL-cell hyperplasia to carcinoids at the end of their normal life span during administration with 14-140 mg/kg/day of omeprazole. No metastasis developed. No carcinoids developed during 18 months high dose treatment of mice (14-140 mg/kg/day). Similarly, administration of omeprazole up to 28 mg/kg/day in dogs for 12 months did not cause any carcinoids.

The gastric carcinoids in rats were related to sustained hypergastrinemia secondary to acid inhibition and not to omeprazole per se.

Short-term treatment (and long-term treatment in a limited number of patients for up to 5 years) to date, have not resulted in any significant pathological changes in gastric oxyntic endocrine cells.

Drug Interactions: LOSEC is metabolized in the liver. This occurs via the cytochrome P-450 system. The pharmacokinetics of the following drugs which are also metabolized through the cytochrome P-450 system have been evaluated during concomitant use of LOSEC in humans: aminopyrine, antipyrine, diazepam, phenytoin, warfarin, theophylline, and propranolol.

Aminopyrine and Antipyrine: After 14 days administration of 60 mg LOSEC once daily, the clearance of aminopyrine was reduced by 19%; the clearance of antipyrine was reduced by 14%. After 14 days administration of 30 mg once daily, no significant changes in clearance were noted.

Diazepam, Phenytoin and Warfarin: Following repeated dosing with LOSEC 40 mg once daily, the elimination half-life of diazepam was increased by 128%; the elimination half-life of phenytoin was increased by 27%. Concomitant administration of LOSEC 20 mg had no effect on plasma concentrations of the (S)-enantiomer of warfarin, but caused a slight, though statistically significant increase (12%) in the less potent (R)-enantiomer concentrations. A small but statistically significant increase (11%) in the anticoagulant effect of warfarin was also seen.

Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with LOSEC.

Theophylline and Propranolol: No effects on oral or I.V. theophylline kinetics have been observed after repeated once daily doses of 40 mg LOSEC. Similarly, no effects on propranolol kinetics were observed in a steady-state trial with 20 mg of LOSEC daily.

Adverse Reactions:

LOSEC is well tolerated. Most adverse reactions have been mild and transient and there has been no consistent relationship with the treatment. Adverse reactions have been recorded during controlled clinical investigations in 2448 patients exposed to LOSEC. In a controlled clinical trial comparing LOSEC to placebo, the prevalence of adverse events with LOSEC 40 mg once daily was similar to the placebo group. In short term comparative double-blind studies with histamine H_2-receptor antagonists, there was no significant difference in the prevalence of adverse events between LOSEC and the H_2-receptor antagonists.

The following adverse experiences (at a rate of more than one percent) have been reported in individuals receiving LOSEC therapy in controlled clinical situations: nausea (3.6%); headache (2.6%); diarrhea (2.9%); constipation (1.4%); abdominal pain (2.0%); dyspepsia (2.2%); flatulence (2.4%) and vomiting (1.9%). Skin rash has occurred in a few patients.

An extensive evaluation of laboratory variables has not revealed any significant changes during LOSEC treatment which are considered to be clinically important. Laboratory abnormalities were reported as serious adverse events in 0.2% (13/7356) *healthy subjects and patients* exposed to LOSEC. In no case was a causal relationship to the drug established. A slight, clinically insignificant increase in alkaline phosphatase S-ASAT and S-ALAT has been observed. Similar increases were also observed with histamine H_2-receptor antagonist treatments in comparative studies.

Symptoms and Treatment of Overdosage:

To date, there is no experience with deliberate overdosage. Single doses of up to 160 mg have been well tolerated. Doses of up to 360 mg per day have been used in patients with Zollinger-Ellison Syndrome with no serious adverse effects. As in all cases where overdosing is suspected, treatment should be supportive and symptomatic. Any unabsorbed material should be removed from the gastrointestinal tract, and the patient should be carefully monitored.

The oral LD_{50} of omeprazole in male and female rats and mice was greater than 4000 mg/kg. In dogs, the only sign of acute toxicity was vomiting which occurred at doses of approximately 600 mg/kg.

Dosage and Administration:

Duodenal Ulcer: *Acute Therapy:* The adult oral dose of LOSEC for the treatment of acute duodenal ulcer is 20 mg given once daily. Healing usually occurs within 2 weeks. For patients not healed after this initial course of therapy, an additional 2 weeks of treatment is recommended.

Refractory Patients: In patients with duodenal ulcer refractory to other treatment regimens, 20 mg and 40 mg LOSEC given once daily has been used. Healing is usually achieved within 4 weeks in such patients.

Gastric Ulcer: *Acute Therapy:* The recommended adult dose is 20 mg of LOSEC given once daily. Healing usually occurs within 4 weeks. For patients not healed after this initial course of therapy, an additional 4 weeks of treatment is recommended.

Refractory Patients: In patients with gastric ulcer refractory to other treatment regimens, 40 mg LOSEC given once daily has been used. Healing is usually achieved within 8 weeks.

Reflux Esophagitis: *Acute Therapy:* The recommended adult dose is 20 mg given once daily. In most patients, healing occurs within 4 weeks. For patients not healed after this initial course of therapy, an additional 4 weeks of treatment is recommended.

Refractory Patients: For patients with reflux esophagitis refractory to other treatment regimens, 40 mg LOSEC given once daily has been used. Healing is usually achieved within 8 weeks.

Maintenance Therapy for Duodenal, Gastric Ulcers, and Reflux Esophagitis: Experience with the long term administration of LOSEC to patients is limited and its use as maintenance therapy cannot be recommended until further data is available.

Zollinger-Ellison Syndrome: The dose of LOSEC used in the treatment of Zollinger-Ellison syndrome will vary with the individual patient. The recommended initial dose is 60 mg LOSEC, given once daily. More than 90% of the patients with the severe form of the disease and inadequate response to other therapies have been adequately controlled with doses of 20 mg to 120 mg daily. With doses greater than 80 mg, the dose should be divided and given twice daily. Doses should be adjusted to the individual patient's need and should continue as long as clinically indicated. Doses up to 120 mg t.i.d. have been administered.

Concomitant Antacid Use: Antacids may be used concomitantly if required. There is no influence on the bioavailability of omeprazole with concomitant antacid treatment.

Patients with Renal Insufficiency: No dose adjustment is required (see PRECAUTIONS).

Patients with Hepatic Insufficiency: The daily dose in patients with severe liver disease should, as a rule, not exceed 20 mg (see PRECAUTIONS).

Elderly Patients: The daily dose should, as a rule, not exceed 20 mg (see PRECAUTIONS).

The capsules should be swallowed whole with sufficient water.

Dosage Forms:

LOSEC 20 mg capsules are two-piece hard gelatin capsules with an opaque pink body and an opaque reddish-brown cap. The body is printed '20,' and the cap $^{A}_{OM}$, in black ink.

Fourteen capsules are provided in a high density polyethylene bottle with a child resistant screw cap which contains a desiccant. The capsules should be dispensed in the original container.

REFERENCES:

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2. Sharma, B.K. et al. Optimal dose of oral Omeprazole for maximal 24 hour decrease of intragastric acidity. Gut, 1984, 25, 957-964.

3. Bardhan, K.D. et al. A Comparison of Two Different Doses of Omeprazole Versus Ranitidine in Treatment of Duodenal Ulcers. J. Clin. Gastroenterol. 1986: (4): 408-413.

4. Walan, A. et al. Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. New Eng. J. of Medicine, Vol. 320 No. 2 Jan. 89 (69-75).

5. Sandmark, S. et al. Omeprazole vs. Ranitidine in the Treatment of Reflux Esophagitis. Scand. J. Gastroenterol 1988: 23: 625-32.

6. Omeprazole Monograph, AB Astra, 1988.

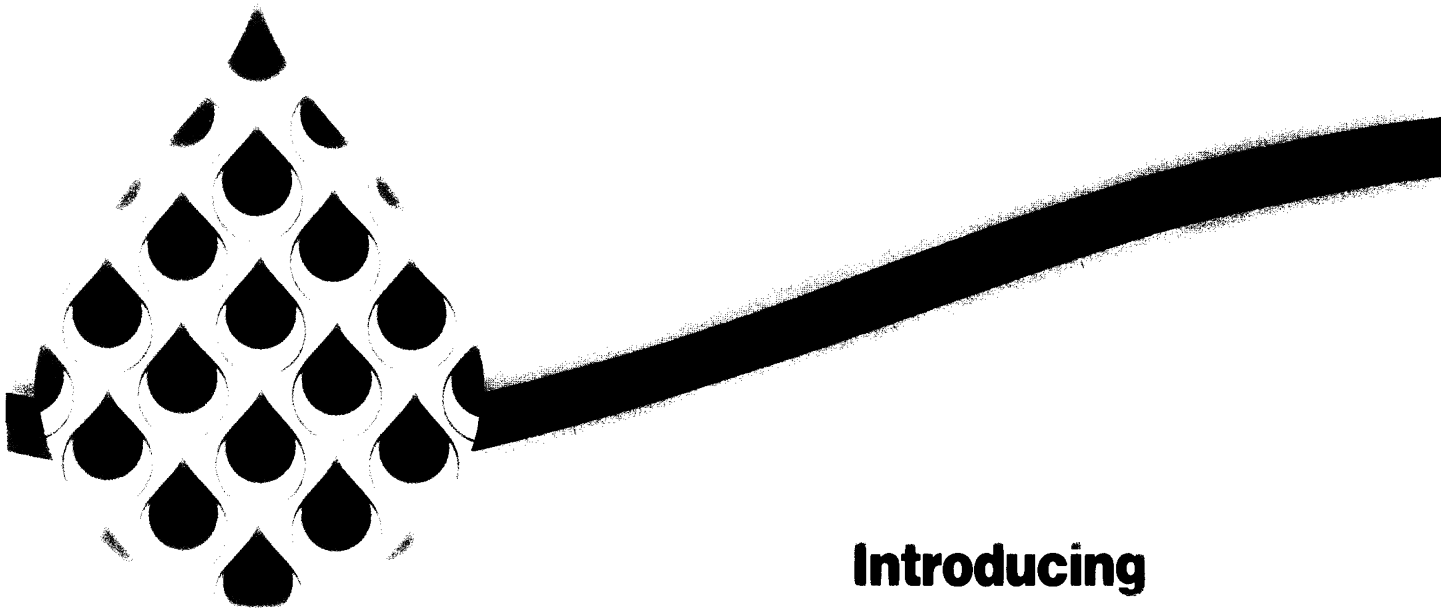
Full Product Monograph available on request from:

ASTRA PHARMA INC.
1004 Middlegate Rd., Mississauga, Ontario L4Y 1M4

PAAB CCPP

Date of preparation: June 7, 1989

Beat the heat. Fit the spot. Skip the mess.



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DuoDERM
CGF

The new wave in wound management.

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Canadian Medical Association

122nd Annual Meeting
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Scientific Program

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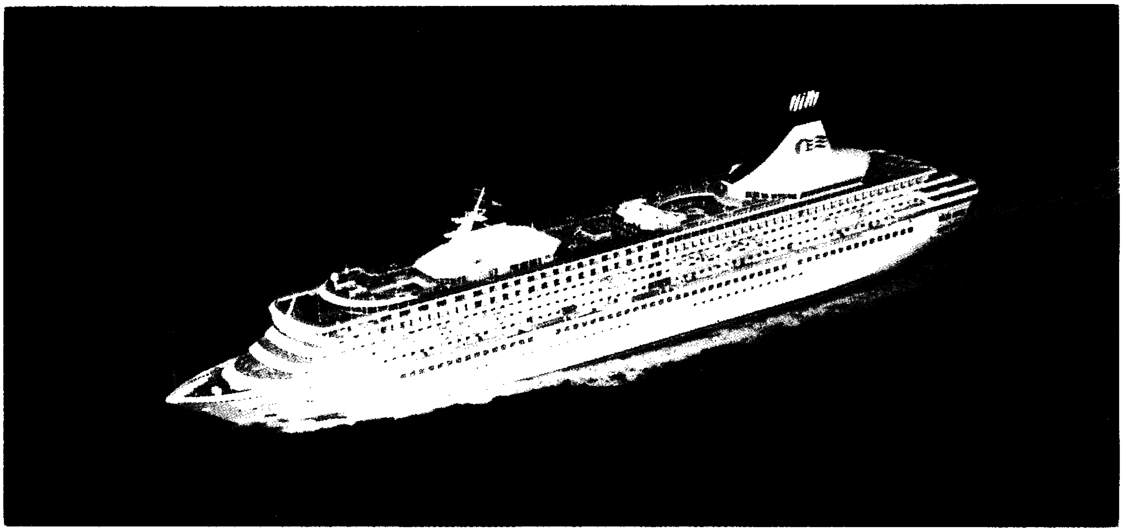
122ieme Reunion annuelle
et
Programme scientifique



GRAND PRIZE DRAWING

Mediterranean & Black Sea Air/Sea Cruise

[illegible] join us in the Scientific Program [illegible] 122nd Annual Meeting [illegible] Quebec City, August 23-25, 1989. By participating in the Program and visiting our exhibitors, you [illegible] eligible to enter [illegible] draw [illegible] Grand Prize.

[illegible] grand prize [illegible] including airfare [illegible] nights aboard the [illegible] Princess [illegible]

* Venice, Italy * Dubrovnik [illegible]
* Crete, Greece * Ephesus [illegible]
* [illegible] Turkey [illegible]
* Odessa [illegible] USSR [illegible] Mykonos [illegible]
* Athens [illegible]

[illegible] participant [illegible] for each full-day session attended [illegible] registration [illegible] Friday, August [illegible] 1989 [illegible]

See you in Quebec City.

[illegible] Grand Prize [illegible] being provided by

INTRAV

[illegible]

TIRAGE GRAND PRIX

Croisière en Méditerranée et en Mer Noire

Prenez part au programme scientifique de [illegible] 122ieme Assemblee annuelle a Quebec [illegible] 25 août 1989. En participant [illegible] dant visite a nos exposants vous [illegible] admissible au tirage de notre [illegible] agit d une croisiere pour deux [illegible] compris le transport aerien et [illegible] du luxueux paquebot *Princess* [illegible] avec escales:

* Venise (Italie) * Dubrovnik (Yougo[illegible])
* Crete (Grece) * Ephese (Turquie)
* Istambul (Turquie) * Yalta (URSS)
* Odessa (URSS) * Mykonos (Grece)
* Athenes (Grece) * Naples (Italie)

Vous recevrez un bulletin de participation [illegible] chaque seance d une journee a laquelle vous assisterez. Ce(s) bulletin(s) se trouve[illegible] dans le materiel de conference qui vous sera remis a l inscription. Le tirage aura lieu dans [illegible] salle d exposition le vendredi 25 [illegible]

Au plaisir de vous voir à Quebec

NOTA: Croisiere offerte [illegible]

INTRAV

organisateur de voyages de [illegible]

CAPOTEN®
(captopril)

Efficacy patients can feel good about

Tablets 25, 50 and 100 mg
Angiotensin Converting Enzyme Inhibitor

INDICATIONS: FOR THE TREATMENT OF ESSENTIAL OR RENOVASCULAR HYPERTENSION. It is usually administered in association with other drugs, particularly thiazide diuretics. The blood pressure lowering effects of captopril and thiazides are approximately additive. In using CAPOTEN (captopril), consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). **a) In patients with normal renal function.** CAPOTEN should normally be used in those patients in whom treatment with diuretic or beta-blockers was found ineffective or has been associated with unacceptable adverse effects. CAPOTEN can be tried as an initial agent in those patients with severe hypertension or in those in whom the use of diuretics and/or beta-blockers is contraindicated or in patients with medical conditions in which those drugs frequently cause serious adverse effects. **b) In patients with impaired renal function.** In these patients, particularly those with collagen vascular disease, captopril should be reserved for hypertensives who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations (see WARNINGS). CAPOTEN is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

CONTRAINDICATION: Contraindicated in patients with a history of hypersensitivity to the drug.

WARNINGS: Proteinuria: Total urinary proteins greater than 1 g per day were seen in <1% of patients receiving CAPOTEN (captopril), but this has been predominantly in those who had prior renal disease, or in those receiving relatively high doses (>150 mg per day), or both. In patients without prior evidence of renal disease the incidence of proteinuria was 0.5%. In these patients receiving ≤150 mg per day, the incidence was 0.2%. Parameters of renal function, such as BUN and serum creatinine were seldom altered in patients with proteinuria. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. Nephrotic syndrome occurred in about one-fifth of proteinuric patients. Membranous glomerulopathy was found in biopsies taken from some patients. A causal relationship to CAPOTEN has not been established since pre-treatment biopsies were not available. Membranous glomerulopathy has been known to occur in hypertensive patients not receiving CAPOTEN. In most cases of proteinuria occurred by the eighth month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses greater than 150 mg per day should have urine protein estimated (dip-stick on first morning urine specimen or 24-hour urine) prior to therapy, at approximately monthly intervals for the first nine months of treatment, and periodically thereafter. When proteinuria is present, 24-hour quantitative determinations provide greater precision. For patients who develop proteinuria exceeding 1 g/day, or proteinuria that is increasing, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis: Neutropenia (<1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient: In clinical trials in patients with hypertension who have normal renal function (serum creatinine <1.6 mg/dL and no collagen disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk of neutropenia in clinical trials was about 1 per 500, a frequency of over 15 times that for uncomplicated hypertension. Daily doses of captopril were relatively high in these patients, particularly in view of their diminished renal function. In patients with renal failure, use of allopurinol concomitantly with captopril has been associated with neutropenia. In patients with collagen vascular disease (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. About half of the reported cases had serum creatinine >1.6 mg/dL and more than 75% were in patients also receiving procainamide. In heart failure, it appears that the same risk factors for neutropenia are present. The neutropenia has been detected within 3 months after captopril was started. Bone marrow examinations in patients with neutropenia consistently showed myeloid hypoplasia, frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypo-plastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. In general, neutrophils returned to normal about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. Evaluation of the hypertensive or heart failure patients should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2 week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after assessment of benefit and risk, and then with caution. Patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, white cell counts should be performed without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count 1000/mm³), the physician should withdraw captopril and closely follow the patient's course. Since captopril decreases aldosterone production, elevation of serum potassium may occur rarely, especially in patients with renal failure (see PRECAUTIONS – Drug Interactions).

Hypotension: Excessive hypotension was seen in hypertensive patients but is a possible consequence of captopril use in severely salt/volume depleted persons such as those treated vigorously with diuretics, for example, patients with severe congestive heart failure (see PRECAUTIONS – Drug Interactions). In heart failure, where the blood pressure was either normal or low, decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and produces either no symptoms or brief mild lightheadedness, although in rare instances, it has been associated with arrhythmia or conduction defects. Hypotension was the reason for discontinuation of drug in 3.6% of patients with heart failure. BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER CLOSE MEDICAL SUPERVISION. A low starting dose may minimize the hypotensive effect (see DOSAGE AND ADMINISTRATION). Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of CAPOTEN, or diuretic, is increased. Hypotension in itself is not a reason to discontinue CAPOTEN. If associated symptoms are troublesome or persist, they are usually relieved by reducing the dose of either CAPOTEN or diuretic.

PRECAUTIONS: Impaired Renal Function: Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine after reduction of blood pressure with captopril. Captopril dosage reduction and/or discontinuation of diuretic may be required. For some, it may not be possible to normalize blood pressure and maintain adequate renal perfusion. About 20% of patients with heart failure develop stable elevations of BUN and serum creatinine 20% above normal or baseline upon long term treatment. Less than 5% of patients, mostly those with severe pre-existing renal disease, [illegible] of treatment due to progressively increasing [illegible] improvement probably depends upon the [illegible] renal disease (see ACTIONS, DOSAGE [illegible] ADVERSE REACTIONS [Altered Laboratory [illegible]

Valvular [illegible] theoretical grounds, that patients with [illegible] valvular risk of decreased [illegible] be [illegible] not developed [illegible] reduction.

Surgery [illegible] undergoing surgery or during anesthesia [illegible] that produce hypotension, captopril may block [illegible] formation secondary to compensatory release of renin. This may be corrected by volume expansion.

Pregnancy: Captopril was embryocidal in rabbits when given in doses 2 to 70 times (on a mg/kg basis) the maximum recommended human dose, and low incidences of craniofacial malformations were seen. The marked embryocidal effect in rabbits was most probably due to the particularly marked decrease in blood pressure caused by the drug in this species. Captopril was also embryocidal in sheep when given in doses similar to those given rabbits. Captopril given to pregnant rats as 400 times the recommended human dose continuously during gestation and lactation caused reduction in pup survival. No teratogenic effects have been observed over larger ranges of captopril were administered to hamsters and rats. The use of the drug in pregnant women has not been established. Since captopril crosses the human placenta, it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Following oral administration, concentrations of unchanged captopril in human milk are approximately 1% of those in maternal blood. The effect of low levels of captopril on the nursing infant has not been determined. Caution should be exercised when captopril is administered to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with the use of captopril in children from 2 months to 15 years of age with secondary hypertension and varying degrees of renal insufficiency. Dosage, on a weight basis, was comparable to that used in adults. CAPOTEN should be used in children only if other measures for controlling blood pressure have not been effective.

DRUG INTERACTIONS: Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, as well as those on severe dietary salt restriction or dialysis, may occasionally experience a precipitous reduction of blood pressure usually within the first hour after receiving the initial dose of captopril (see WARNINGS). When feasible the hypotensive effects may be minimized by either discontinuing the diuretic or increasing the salt intake approximately one week prior to initiation of treatment with CAPOTEN. Alternatively, provide medical supervision for at least one hour after the initial dose. If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. This transient hypotensive response is not a contraindication to further doses which can be given without difficulty once the blood pressure has increased after volume expansion.

Agents Having Vasodilator Activity: Data on the effect of concomitant use of other vasodilators in patients receiving CAPOTEN for heart failure are not available; therefore, nitrates (as used for management of angina) or other drugs having vasodilator activity should, if possible, be discontinued before starting CAPOTEN. If resumed during CAPOTEN therapy, such agents should be administered cautiously, perhaps at lower dosage.

Agents Causing Renin Release: Captopril's effect will be augmented by antihypertensive agents that cause renin release. For example, diuretics (e.g., thiazides) may activate the renin-angiotensin-aldosterone system.

Agents Affecting Sympathetic Activity: The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Therefore, agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) should be used with caution. Beta-blocking drugs add some further hypotensive effect to captopril, but the overall response is less than additive. In heart failure, special caution is necessary since sympathetic stimulation is a vital component supporting circulatory function and inhibition with beta-blockade always carries a potential hazard of further depressing myocardial contractility.

Agents Increasing Serum Potassium: Since captopril decreases aldosterone production, elevation of serum potassium may occur. Potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Salt substitutes which contain potassium should also be used with caution.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Inhibitors of Endogenous Prostaglandin Synthesis: It has been reported that indomethacin may reduce the antihypertensive effect of captopril, especially in cases of low renin hypertension. Other non-steroidal anti-inflammatory agents (e.g., aspirin) may also have this effect. The blood pressure lowering effects of captopril and beta-blockers are less than additive. In patients with renal failure, the use of allopurinol concomitantly with captopril has been associated with neutropenia. In patients with heart failure, the use of procainamide concomitantly with captopril has been associated with neutropenia.

Information for Patients: Patients should report promptly any indication of infections (e.g., sore throat, fever), which may be a sign of neutropenia, or of progressive edema, which might be related to proteinuria and nephrotic syndrome. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician. Warn patients against interruption or discontinuation of antihypertensive medications without the physician's advice. Patients treated for severe congestive heart failure should be cautioned to increase their physical activity slowly.

SYMPTOMS AND TREATMENT OF OVERDOSAGE. In the event of overdosage, correction of hypotension would be of primary concern. Volume expansion with an intravenous infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis. [illegible] incidences are based on clinical trials involving approximately [illegible] patients.

Rash: Approximately 1% of patients developed pruritic rash (see WARNINGS). Each of these patients has been reported in approximately [illegible] patients and [illegible] in relationship to drug use [illegible] renal failure, [illegible] and urinary frequency.

Hematologic: Neutropenia/agranulocytosis (see WARNINGS). Cases of anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic: Rash occurred in 8.5% of patients with normal renal function and 13% of patients with evidence of prior renal function impairment. It was dose related, having occurred in 7% of patients at doses of ≤150 mg per day. The rash is usually maculopapular, rarely urticarial, and generally occurs during the first 4 weeks of therapy. It is usually mild and disappears within a few days of dose reduction, short term treatment with an antihistamine, or discontinuation of therapy. Pruritus without rash has occurred. [illegible] and 10% [illegible] or positive ANA titers. [illegible] sion, and [illegible]

[illegible] membranes of the mouth, [illegible] in approximately 0.1% of patients and is reversible on discontinuance of captopril therapy. Serum sickness and bronchospasm have been reported. One case of laryngeal edema has been reported.

Cardiovascular: Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations have each been observed in approximately 1% of patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure have each occurred in 0.2 to 0.3% of patients. Flushing or pallor has been reported in 0.2 to 0.5% of patients.

Alterations in Taste: 2% of patients receiving ≤150 mg/day of CAPOTEN developed a diminuation or loss of taste perception. At doses >150 mg per day, 7% of patients experienced this effect. Taste impairment is reversible and usually self-limited (2 to 3 months) even with continued drug administration. Weight loss may be associated with the loss of taste. The following have been reported in about 0.5 to 2% of patients:

Gastrointestinal: gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer.

CNS: dizziness, headache, malaise, fatigue, insomnia, paresthesia.

Others: dry mouth, dyspnea, cough, alopecia, impotence, loss of libido, disturbed vision, and itching and/or dry eyes.

Altered Laboratory Findings: Elevations of liver enzymes have been noted in a few patients but no causal relationship to captopril use has been established. Rare cases of cholestatic jaundice, and of hepatocellular injury with or without secondary cholestasis, have been reported. Elevation of BUN and serum creatinine may occur, especially in patients who are volume-depleted or who have renovascular hypertension. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, resulting in transient rises in serum creatinine and BUN. Small increases in the serum potassium concentration frequently occur, especially in patients with renal impairment (see

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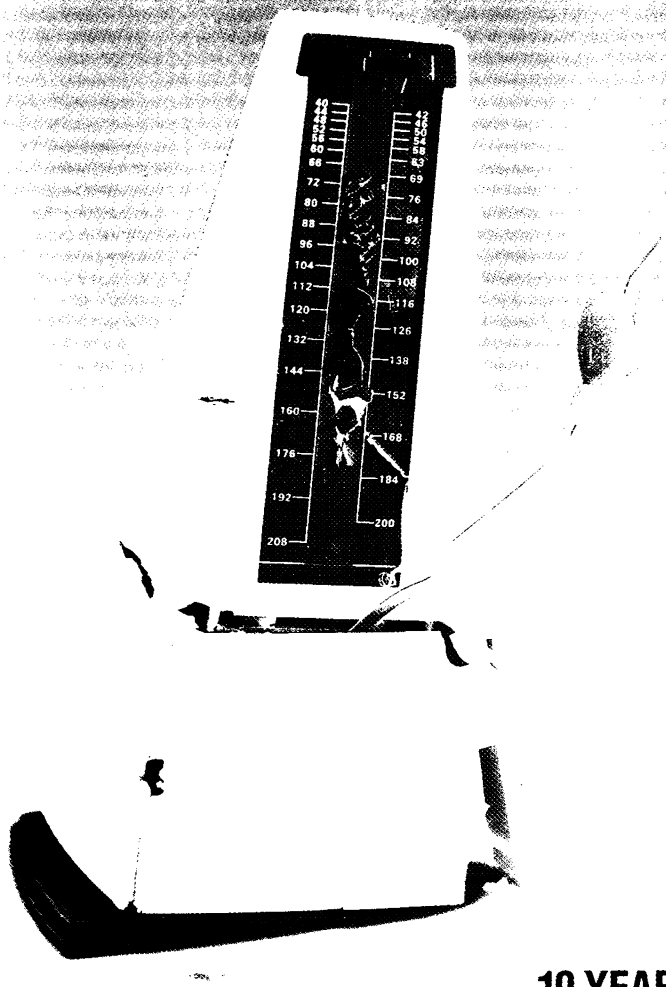

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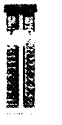

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